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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/020,541	04/26/2002	Larry A. Wheeler	17400(BAR)	1687

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EXAMINER	
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ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/020,541	**Applicant(s)** WHEELER ET AL.	
	Examiner Jon Eric Angell	**Art Unit** 1635	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 29 September 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *16,18-22 and 30*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

JON E. ANGELL, PH.D.
PRIMARY EXAMINER

Continuation of 11. does NOT place the application in condition for allowance because: Applicants argue "[T]he issue is not whether 'what was known in the art' is considered as a whole, but whether the disclosure and suggestions of each prior art reference, and their combination is so considered." In response, the rejection is based on the teaching of a combination of three references: Miller et al. (U.S. Patent Application 2002/0040015), Granville et al. (U.S. Patent No. 6,180,402) and Wheeler et al. (Eur. J. Opthal. 9:S17-S21, 1999).

Applicants argue that the 6/27/2006 Office Action fails to characterize the teachings of the prior art references completely, or entirely accurately. Applicants contend "contrary to the Examiner's contention, Miller does in fact amelioration of adverse effects of of PDT." Applicants further state "On page 11 of the provisional patent application Miller states that different apoptotic pathways are triggered by PDT in bovine retinal capillary endothelial (BRCE) and retinal pigment epithelium (RPE) cells." Applicants also refer to page 11 of the '015 application as stating, "It may be possible to specifically prime the apoptotic machinery of neovascular endithelial cells prior to PDT so as to increase thei sensitivity to PDT.... This approach could reduce the light dose (fluence) necessary to achieve CNS closure and thereby decrease the effect on the surrounding cells such as RPE." In response, it is respectfully pointed out that Applicants appear to be reffering to U.S. Provisional Application 60/181,641 (Miller et al.), which is not the the '015 Miller et al. reference because the cited passage is not present on page 11 of the '015 application. It appears that the quoted passage appears on page 11 of provisional application 60/181,641. Therefore, the Examiner does not believe that the prior art references have not been completely or entirely accurately characterized.

Applicants argue that Miller teaches "that apoptosis is a cell-specific phenomenon and suggests taking advantage of this discrepency between different cell types' susceptibility to apoptosis triggered PDT". In response, Miller et al., at best suggests that different apoptotic pathways may be triggered by PDT in BRCE and RPE cells. This suggestion does not bring into question whether or not an antiapoptotic neuroprotective agent which which was known to cause overexpression of bcl-2 (such as brimonidine) would inhibit apoptosis in neural tissues.

Applicants argue that Miller is silent with regard to neural cells or neuroprotection. In response, it is repectfully pointed out that the 6/27/2006 Office action indicated that the Miller provisional application (i.e., 60/181,641) explicitly teaches, "The anti-angiogenesis factor can potentiate the cytotoxity of the PDT. The potentiation may result in enhanced occlusion of the choroidal neovasculature. In addition, the anti-angiogenesis factor can enhance the selectivity of photodynamic therapy, for example, by permitting occlusion of the choroidal neovasculature while at the same sparring surrounding blood vessels, for example, normal choroidal vasculature, and/or tissue, for example, the overlaying neurosensory retina." (See page 3). Therefore, the Miller provisional application does specifically disclose "sparring... the overlaying neurosensory retina" which not only suggests, but actually teaches that neuroprotection in PDT is desired.

Applicants acknowledge that Granville does indeed teach the use of antiapoptotic agents in conjunction with PDT to treat "adverse effects" of PDT. Applicants contend that Granville does not discuss what the adverse effects are, nor does Granville contemplate the use of a neuroprotectant or protecting neural cells specifically. Applicants also argue that Wheeler does not that brimonidine is effective for treating optic nerve atrophy, nor does Wheeler suggest PDT. In response, it appears that Applicants argue the references individually. Applicants are reminded that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, the rejection is based on the combination of the Miller et al., Granville et al. and Wheeler et al. references. It is acknowleged that Granville does not teach using a neuroprotectant or specifically protecting neural cells. However, Granville does teach that PDT has adverse side effects and the Miller provisional application teaches that protection of neural cells would be desirable. Wheeler et al. teaches that brimonidine is a neuroprotective antiapoptotic agent which could be used to inhibit apoptosis in neural cells. Therefore, it would have been prima facie obvious to one of ordinary skill in the art to use an antiapoptotic neuroprotective agent such as brimonidine in conjunction with PDT in order to ameliorate adverse side effects (i.e., apoptosis) of neural tissue caused by PDT when PDT is applied as an eye treatment.

Applicants argue that the Office Action attempts to make out a prima facie case of obviousness based on hindsight-based "pick and chose" analysis. In response, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Furthermore, when considering the teachings of the cited references which exemplify the level of ordinary skill at the time of filing, there is a suggestion or motivation to combine the reference teachings and there would have had a reasonable expectation of success. Specifically, Miller et al. teaches that PDT can be used to treat neovascularization of the eye, and one of ordinary skill in the art would recognize that this could result in neural damage; Granville et al. provides a suggestion or motivation that using an antiapoptotic agent (such as an agent that increases bcl-2 expression) in conjunction with PDT can ameliorate the adverse effects of the PDT; Miller et al. teaches that PDT can be used to treat neovascularization of the eye, and one of ordinary skill in the art would recognize that this could result in neural damage; and Wheeler et al. teaches that brimonidine is an antiapoptotic neurprotectant which causes increased bcl-2 expression. Therefore, one of ordinary skill in the art, at the time of filing, would have sufficient knowledge and motivation to combine the teachings of Miller et al., Granville et al., and Wheeler et al. to make the claimed invention. Furthermore, the teaching of Wheeler et al. that brimonidine increases bcl-2 expression and inhibits apoptosis, provides a reasonable expectation of success that brimonidine could be used as an antiapoptotic neuroprotectant to protect neural cells from adverse effects of PDT treatment of neovascularization in the eye.

Applicants argue that the combination of references do not teach each and every limitation of the claims. Specifically, applicants

argue that claim 16 encompasses a method of protecting ocular neural tissue from damage caused by PDT comprising delivering an amount of brimonidine effective to protect a plurality of ocular neurons from damage as compared to the degree of ocular neuron cell death observed in the absence of said amount of brimonidine. Applicants assert that the combined references do not teach this comparative step. In response, it is respectfully pointed out that the phrase "compared to the degree of occular neuron cell death observed in the absence of said amount of brimonidine" does not impart any particular active methods steps. That is, the indicated phrase is considered functional language describing the necessary result of performing the actual active method steps recited in the claims. Since the combined teachings of the cited prior art provides a suggestion or motivation to perform the claimed method steps, the results must be the same as the results of the claimed method. Applicants also argue that claims are drawn to intraocular and intravitreal injection of brimonidine and such limitation is nowhere to be seen. In response it is respectfully pointed out that Miller et al. teaches that delivery can be by any mode of administration (e.g., see paragraphs 69-70), and specifically teaches intravenous administration and intravitreal administration. Furthermore, it would have been a matter of routine optimization to identify the most effective route of administration. As noted in In re Aller, 105 USPQ 233 at 235, "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." Therefore, routine optimization is not considered inventive and no evidence has been presented determining effective routes of administrationwas other than routine or that the results obtained using the different routes of administration should be considered unexpected in any way as compared to the closest prior art. Applicants also argue that claim 30 is drawn to using brimonidine in combination with an antiangiogenic compound, which has ot been identified as being taught in the cited references. In response, it is respectfully pointed out that Miller teaches using PDT in combination with an antiangiogenic compound (e.g., see abstract). Therefore, the combination of Miller, Granville and Wheeler provide a prima facie case of obviousness for the claimed invention, including using PDT in combination with brimonidine and an antiangiogenic compound.

Applicants argue that Miller teaches away from the claimed invention because it offers a different solution for preventing harm to surrounding cells and does not contemplate using an apoptosis antagonist. In response, the Examiner respectfully disagrees with Applicants contention that Miller teaches away from using an anti-apoptotic molecule such as the neuroprotectant brimonidine in conjunction with PDT because: (1) the Miller's '641 provisional application is silent with respect to using an anti-apoptotic agent as a neuroprotectant; and, (2) the '641 provisional application only contemplates using a pro-apoptotic agent to enhance the cytotoxic effect of PDT specifically in the target neovasculature (see the specific passages of the '641 application cited by the applicants on page 7 of the 4/3/06 response). It is the Examiner's position that teaching the use of an apoptosis-inducing agent in conjunction with PDT in order to enhance the cytotoxic effects of the PDT in neovasculature tissue does not teach away from using PDT in conjunction with an anti-apoptotic agent wherein the anti-apoptotic agent is used as an agent to protect the non-target tissue, such as the neural tissue, which could be damaged by PDT treatment.

Applicants argue that assuming that the combined references suggest attempting the present invention, the suggested method would only be "obvious to try" and there would not be a reasonable expectation of success. Applicants also assert that it is not clear that the the problem solved by the present invention was recognized by the prior art (i.e., the prior art does not indicate that PDT at less than "high doses" of photosensitizer, or using a photosensitizer other than vertiporfin harms occular neural tissue). In response, it is respectfully pointed out that the instant claims are not limited to using less than high doses of photosensitizer of using a photosensitizer other than vertiporfin. Therefore, applicants appear to be arguing limitations which are not present in the claims. Furthermore, the combined teaching of Miller, Granville and Wheeler (especially Wheeler et al.) provides a reasonable expectation that the antiapoptotic neuroprotectant brimonidine can protect occular neural tissue from damage caused by a photoactive component of PDT compared to the damage observed when brimonidine is not used.

Therefore, Applicants argument are not persuasive.

JON E. ANGELL, PH.D.
PRIMARY EXAMINER